

# Newsletter 21

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## Welcome note



Welcome to the 21<sup>st</sup> issue of our Newsletter where we present our associates in Montenegro and our product Clavomid®.

In Environmental Issues we investigate the use of biodiesel as an alternative fuel, in Health Matters we report on the use and abuse of antibiotics and in the ABC of Pharmacy we continue with the term "Encapsulation". The internal campaign on Health & Safety, the proposal to set up a municipal social pharmacy/medical practice, Easter donations and the appeal by the Cyprus Red Cross are described in Corporate Social Responsibility.

In Remedica News we pay tribute to our late associate in Saudi Arabia, Abdullah Al Hobail, and report on our cooperation with the Cyprus Technical University (TEPAK), the launch of our new anticancer product, participation in the Limassol Marathon and school visits.

Finally, we take a glimpse at the historic monastery of Kykkos. ■

## Remedica Worldwide: Farmegra, Monte Negro



**Farmegra is Remedica's partner in Montenegro, a small country of about 600,000 inhabitants that**

**resulted from the partition of former Yugoslavia: it borders the Adriatic Sea and Bosnia, Albania, Kosovo and Bosnia & Herzegovina. Expenditure on medicines is estimated at around 50 million Euro per year with another 20 million Euro as "over-the-counter" (OTC) pharmaceutical products expenditure. There are several types of healthcare institutions such as clinical centres, regional hospitals, public health centres, private medical practices, private hospitals and both state and private pharmacies.**

Farmegra was established in 1999 as a privately owned, limited liability company, licensed for the wholesale distribution of pharmaceutical and consumer healthcare products. It has 56 employees and has implemented a Quality Management System in accordance with the standards of ISO 9001:2008 in May 2009.

Farmegra distributes more than 4000 products divided into the following product groups:



- local and imported pharmaceuticals
- local and imported OTC and dietary products
- cosmetics

medical devices and disposable products

Its goal is to cover the entire spectrum of pharmaceutical supplies and pharmacy - related services, with its prime focus being on customers such as pharmacies, hospitals and pharmaceutical manufacturers and to retain its position as a leading distributor and service provider in the pharmaceutical arena.

It currently services the entire country in 3 geographical segments:



Remedica began cooperation with Farmegra in 2002 and throughout the last decade the Company's products have experienced constant growth both in the number of products (now 60) and the value of sales. The portfolio includes products from a variety of therapeutic categories like antibiotics, neuroleptics, immunosuppressants and antiepileptics. The fruitful cooperation between the two companies shows all the signs that it is destined to increase in the future. ■

# Our Products: Clavomid®

Clavomid Tablets contain a well-tolerated combination of a broad spectrum  $\beta$ -lactam antibiotic, namely amoxicillin, with a  $\beta$ -lactamase inhibitor, potassium clavulanate. The combination is widely known as Co-amoxiclav and it is used in the treatment of bacterial infections against strains of microorganisms that have developed resistance to  $\beta$ -lactam antibiotics.

Amoxicillin was first developed in 1953 as an orally administered, chemically modified analogue of penicillin which is active against both Gram-positive and Gram-negative bacteria. It acts by interfering with the synthesis of the bacterial wall through inhibition of the transpeptidase that enables the formation of the peptidoglycan structure

of the wall, resulting in cell lysis and the death of the organism; this is known as bactericidal action. Like many penicillins, amoxicillin is inactivated by certain  $\beta$ -lactamase enzymes and therefore is rendered ineffective against organisms which produce such enzymes (Dollery, 1999).

The co-administration of clavulanic acid with amoxicillin extends its activity by protecting the drug from the hydrolytic action of  $\beta$ -lactamases but only if they have a nucleophilic serine residue in the active site (Brown *et al.*, 1996). In addition to its primary action, clavulanic acid has been found to enhance the action of amoxicillin in non- $\beta$ -lactamase-producing strains of bacteria both *in vitro* and *in vivo*, by

enhancing the killing capacity of human polymorphonuclear cells (Finlay *et al.*, 2003).

Co-amoxiclav oral preparations are indicated for the short-term treatment of:

- *Upper Respiratory Tract (Ear, Nose and Throat) Infections (including Ear, Nose and Throat infections)* in particular sinusitis, otitis media, recurrent tonsillitis.

- *Lower Respiratory Tract Infections* in particular acute exacerbations of chronic obstructive pulmonary disease (bronchitis) especially if considered severe, bronchopneumonia.

- *Genito-urinary Tract and Abdominal Infections* in particular cystitis (especially

when recurrent or complicated but excluding prostatitis), septic abortion, pelvic or puerperal sepsis and intra-abdominal sepsis.

- *Skin and Soft Tissue Infections* especially cellulitis, infected animal bites and severe dental abscess with spreading cellulitis.

- Mixed infections caused by amoxicillin-susceptible organisms in conjunction with Co-amoxiclav-susceptible  $\beta$ -lactamase-producing organisms.

Remedica Ltd has developed Co-amoxiclav Tablets under the trade name Clavomid. The tablets are film-coated and contain two strengths of the antibiotic, 250 or 500mg, each combined with 125mg of clavulanic acid.



## References:

- Brown, R. P., R. T. Aplin and C. J. Schofield (1996). "Inhibition of TEM-2 beta-lactamase from Escherichia coli by clavulanic acid: observation of intermediates by electrospray ionization mass spectrometry." *Biochemistry*, **35**(38): 12421-32.
- Dollery, C. (1999). *Therapeutic Drugs*. CD-ROM Database. Release 1.0. Edinburgh, Churchill Livingstone, Distributed by Harcourt Brace and Company Ltd.
- Finlay, J., L. Miller and J. A. Poupard (2003). "A review of the antimicrobial activity of clavulanate." *J Antimicrob Chemother*, **52**(1): 18-23. ■

# The ABC of Pharmacy:

## Encapsulation

About 80% of modern medicines are taken orally in the form of tablets (which were dealt with in the last issue of the Newsletter) and capsules. Both are solid dosage forms which are convenient for the patient to swallow and have good stability profiles. Capsules are available in hard and soft forms, and although both consist of the Active Pharmaceutical Ingredient (API) enclosed in a gelatin-based capsule shell, the former are the easiest to manufacture and the most popular with patients. Soft gelatin capsules are used to encapsulate liquid APIs and can only be produced on purpose built machines so their manufacture is usually contracted out to specialists.

Hard capsules are produced from gelatin as two cylindrical halves each with one closed end: one half (the body) has a slightly smaller diameter which allows the larger part (the cap) to fit snugly over the body. The capsule shells are made by dipping pins into solutions of hot gelatin to which dyes or pigments can be added so that each half of a capsule may be a different colour which helps in identification and branding. A name, code, strength or logo can also be printed on the shell if required. Specialist companies produce capsule shells using machines that can produce up to 1 million capsules per day, for supply to the pharmaceutical industry who then fill them with their own formulations. The shells are commonly available in 5 different volumes (sizes) which allow products of varying doses to be produced: the largest dose is of the order of 500mg since this is the biggest capsule that can be swallowed.

Although small quantities of capsules can be made by hand, the manufacture of large batches is carried out on a multi-station (semi-) automatic machine. Modern machines are

able to separate the two parts of the empty capsule shell, secure the body in an upright position so that the formulation (powder, granule, pellet) can be inserted and then push the cap over the body to make a sealed unit. The dose can either be measured by completely filling the body of the capsule or by means of a measuring device. Modern machines can produce as many as 150,000 filled capsules an hour.

Most APIs are formulated as powders and the production of a material with optimum flow properties is crucial. The larger the dose of the API then the more difficult this may become since it will take up most of the space within the capsule and there will be little opportunity to include other excipients. Fortunately few APIs interact with the gelatin film and only those which can induce cross-linking or affect the water content of the shell definitely need to be avoided. The excipients which are used are very similar to those used in tablets and include diluents (increase the bulk of the contents), disintegrants (promote breakup of the capsule after swallowing), lubricants and glidants (improve the flow properties of the powder). The particle size of the API is one of the most significant factors to be considered in the formulation process since it can adversely affect the performance of the product if it is either too small or too large.

The effect that a capsule produces can be further modified by, for example, the application of a coating which is resistant to acid so that it will not break up to release the contents until it has passed through the stomach. By the use of such techniques it has even been claimed that drugs can be targeted to the colon (large bowel). ■







# Environmental Issues: Biodiesel-an alternative fuel.

According to the European Biodiesel Board, biodiesel may be defined as a renewable fuel that is produced from vegetable oils, used frying oils or animal fats. Biodiesel is produced commercially from rapeseed, sunflower seed or soybean oils or from the recycling of used frying oils. Biodiesel is considered to be a cleaner replacement for petroleum diesel fuel as it is non toxic, biodegradable and less polluting.

Although biodiesel can be used in its pure form, it can also be used as a blend along with petroleum diesel in mixtures of 5% or 20%. In fact, according to the United States Department of Energy, the mixture of 20% biodiesel and 80% petroleum diesel, referred to as B20, is the most common biodiesel mixture in that country. This is mainly due to the fact that B20 and lower blends of biodiesel do not require engine modifications. As the United States Department of Energy suggests, engines running on B20 perform similarly to engines running on petroleum diesel, including horsepower, torque and fuel consumption. The use of 100% biodiesel however, would require modifications to the vehicle engine and although this would make the fuel a viable option it will undoubtedly result in reduced power and there are still some concerns regarding the long-term impact on engine durability.

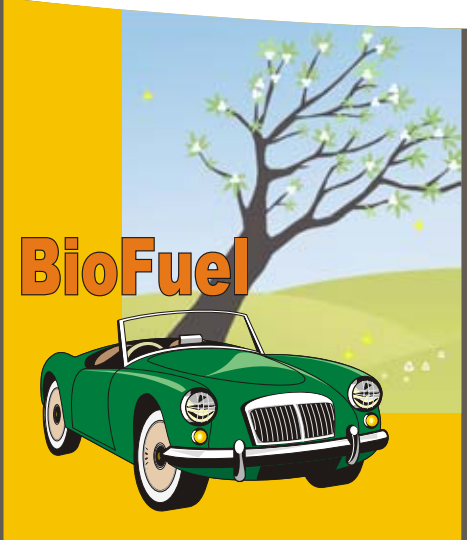
The use of biodiesel as a transport fuel comes with numerous advantages. As mentioned above, biodiesel can be produced locally either from vegetable crops or the recycling of fried oils and therefore has the potential to boost national energy security by reducing importation of petroleum oil.



In addition, engines run on biodiesel are far less polluting, compared with conventional petroleum engines, especially in terms of carbon dioxide and particulate emissions and according to the US Environmental Protection Agency B100 and B20 reduce carbon dioxide emissions by more than 75% and 15% respectively. In other words, biodiesel, if widely used, could contribute significantly to the tackling of global climate change and local air pollution. In addition, biodiesel is biodegradable, non-toxic and is safer to handle, store and transport as it has a much higher flashpoint compared with petroleum fuels making it considerably less flammable.

Despite its numerous potential advantages, biodiesel has not yet been introduced widely mainly due to the obstacles of availability and cost. More importantly, more development needs to be carried out by the automotive industry in order to produce engines that can run efficiently on higher blends of biodiesel.

Finally, if as predicted by the European Environment Agency, up to 15% of energy demand in 2030 could be provided by bioenergy produced by local resources in the European Union then biodiesel could play a vital role in achieving these targets. ■



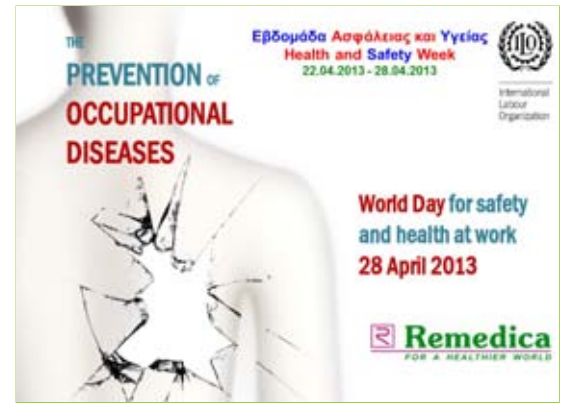
# Corporate Social Responsibility: Remedica Cares

## 1) Health & safety week. (photo 1, 2)

In its ongoing efforts to promote health & safety and to prevent accidents, Remedica carried out an internal campaign into various activities including the safe use of ladders, the correct use of fire extinguishers, working high above ground, safe use of machines with moving parts, using hazardous chemicals and flammable materials, avoiding dangers from electrical power and lifting items properly. Staff were also reminded of the value of prompt but proper first aid as a means of limiting damage should an accident occurs. Emphasis was also given to preventive measures and safety practices as well as the use of protective equipment. Finally, specific attention was paid to the adoption of good practices which can prevent or reduce occupational diseases. Each day was devoted to a different topic and the relevant presentation was also uploaded onto the company's intra net so that employees could review and revisit them as necessary.

## 2) Municipal Social Pharmacy / Medical Practice.

Remedica was represented at a meeting called by the Mayor of Limassol attended by all relevant people for a first briefing on the proposal to set up a Municipal Social Pharmacy-Medical Practice. Remedica responded to the municipality's call to contribute to society in these difficult times that Cyprus is going through by offering to either donate pharmaceutical products or discount those that are very expensive. In addition, participating doctors will not



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be charging patients for consultations. All participants undertook to submit final proposals on the issue to the Mayor.

## 3) Easter donations. (photo 3)

At Easter, as in previous years, Remedica assisted several charitable organisations by purchasing Easter candles, which were then given free to its staff. This year the 3 associations to benefit were: the Day Centre for People with Special Needs (Prosvasi), the Theotokos Foundation and the Cyprus Association of Cancer Patients and Friends.

## 4) Pan-Cyprian door-to-door collection by the Cyprus Red Cross. (photo 4, 5)

This annual charity collection was held in order to raise funds for the various programmes and missions of the Cyprus Red Cross, both locally and abroad. Once again, Remedica was pleased to contribute to these efforts in the form of a financial donation. ■



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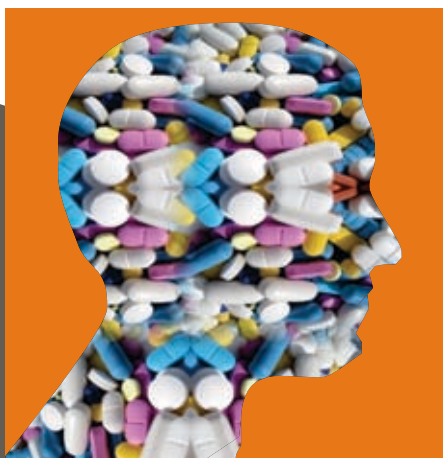


"DOOR TO DOOR" FUNDRAISING CAMPAIGN  
Open your door to the Red Cross

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# Health Matters:

## Antibiotics: Use and Abuse



Antibiotics are a group of drugs which are used to fight various infections caused by microorganisms to which they are selectively toxic and do not, or should not, harm cells of the host. The choice of the most appropriate treatment is based on the sensitivity of the microorganism towards different antibiotics. Antibiotics can act either by direct killing of a microorganism or by helping the immune system to defend itself against the infecting microorganisms (e.g. by stopping or slowing their growth).

Antibiotics can be divided into seven categories according to their chemical structure, as well as by the way in which they act. These categories are: penicillins, cephalosporins, tetracyclines, aminoglycosides, macrolides, fluoroquinolones and others which do not have a specific structure or action.

Also, based on the spectrum of microorganisms against which a specific antibiotic category is therapeutically effective, the antibiotics can be classified into:

- A) *narrow spectrum antibiotics*, that are only active against one microorganism or a small group of microorganisms.
- B) *spread-spectrum antibiotics*, which are active against gram-positive microorganisms and a significant number of gram-negative bacteria.
- C) *broad-spectrum antibiotics*, which are active against a wide variety of microbial species.

Most modern antibiotics are absorbed after oral administration but the parenteral route (e.g. intravenous) route is used for those that are poorly absorbed from the gastrointestinal tract, as

well as for cases of serious infections where high concentrations of antibiotic need to be maintained in the serum.

During the last 4 to 5 decades, more and more examples of microorganisms that have developed resistance to antibiotics have been found. A microorganism is called resistant when its growth is not inhibited by the maximum concentration of the antibiotic that can be tolerated by a patient. Perhaps the best known and notorious example is methicillin resistant *Staphylococcus aureus* (MRSA) which, once it occurs, is extremely difficult to eradicate.

Many microorganisms have the ability either to genetically mutate, or develop the ability to produce specific enzymes that can destroy or inactivate the antibiotic. The main reason for the development of resistance is the irrational use of antibiotics, leading to the increase of patient morbidity and mortality year by year, since the infections caused by resistant microorganisms are often very serious and life-threatening. The use of antibiotics to promote growth in animals which enter the food chain is another cause of resistance. It is estimated that 37,000 European citizens die every year from nosocomial (hospital-acquired) infections caused by

resistant microorganisms, while the annual cost of hospital treatment amounts to 5.5 billion euros.

Scientists from all over the world have already sounded the alarm bells. They emphasise that if the irrational use of antibiotics continues, the inevitable concomitant increase in bacterial resistance will mean that even simple infections could lead to pandemics and the situation will be exacerbated by the noted decline in the discovery and licensing of new antibiotics. Immediate measures at personal, national and global levels should be taken as soon as possible. At a personal level, the use of antibiotics should be avoided without medical advice. Large numbers of patients take antibiotics when they have been infected by viruses (e.g. seasonal influenza) and not by bacteria. It is, of course, well known that antibiotics have no therapeutic efficacy against viral infections (although they may be required to treat any secondary bacterial infection which may subsequently develop as a result). Also the patients should ensure that they finish taking the full course of any prescribed antibiotics (typically 7 -14 days or more) and not stop once the symptoms seem to have subsided. This will ensure that all the

infecting microorganisms are killed and will not linger to spread the disease. The resistance of *Salmonella enteritidis* to quinolone antibiotics was found to have increased 10-fold in just 5 years following the increase in its use in animals used as food (Molbak et al, 2002). At national and international level, the development of a tighter institutional and legislative framework for the prescription and use of antibiotics seems to be more than ever imperative. It has become part of local antibiotic policies in some countries to reserve a few of the more potent antibiotics to treat resistant infections so that they do not become the subject of resistance themselves. The importance of this topic has been formally recognised by the EU which published a 5 year 'Action plan against the threats from rising Antibiotic Resistance' in 2011.

### Bibliography:

Molbak, K., P. Gerner-Smidt and H.C. Wegener (2002), "Increasing quinolone resistance in *Salmonella enterica* serotype Enteritidis", *Emerging Infectious Diseases* 8(5): 514-515.

Richard A. Harvey, Pamela C. Champe, Pharmacology- Third edition-Greek version, 2007. ■



# Remedica News

## 1) Obituary: Abdullah Al Hobail.

It is with great sadness that we report the death of Mr Abdullah Al Hobail, General Manager of Al Hobail Medical Office Company in the Kingdom of Saudi Arabia from an incurable disease which he had been fighting during the past few years. Despite one year of treatment in the US he could not defeat the disease and passed away in his homeland.

Abdullah Al Hobail was a close and respected associate of Remedica. His company was responsible for the registration of Remedica and many of the Company's products in the Kingdom of Saudi Arabia, establishing a business with a turnover of more than a million dollars per year. His son, Mr Mohammed Al Hobail, will succeed Mr Abdullah as General Manager and Mr Waleed Al Hobail will become the Deputy General Manager of the Al Hobail Medical Office Company.

The Board and staff of Remedica offer their sincere condolences to his family with whom it is hoped that the successful collaboration inspired by Mr Abdullah will continue to flourish.

## 2) TEPAK cooperation. (photo 1)

The ongoing cooperation between Remedica and the Cyprus Technological University (TEPAK) has been extended by the signing of an agreement for specialised laboratory tests to be carried out. The Microbiology and Biotechnology team in the Agricultural Sciences, Biotechnology and Food Science Department of TEPAK will carry out the advanced molecular biology tests under the supervision of Professor Demetris Tsaltas which will continue until the end of 2013.



## 3) Launch of Imatinib.

Remedica successfully launched Imatinib (a product to treat leukaemia) in the markets of Eastern Europe. The price advantage offered by Remedica's Imatinib will be a relief to national health systems and it means that more patients will be able to benefit from this therapy. Remedica was able to offer this economic advantage by producing a tablet which does not infringe current patents.

## 4) Limassol Marathon. (photo 2, 3)

Remedica supported the 7<sup>th</sup> Limassol International Marathon GSO held on the 24<sup>th</sup> March with a corporate entry of 40 colleagues thereby making a significant contribution to the fund-raising effort. In addition to raising valuable funds for various charities, the Marathon aims to spread spirit of sportsmanship, participation and volunteerism. It is pleasing to note that the Remedica team achieved third place and we would like to congratulate all those who participated and their supporters for their efforts.



## 5) School visits. (photo 4)

The second-year students in the Pharmacy Assistants and the Medical Representatives courses of KES College recently visited Remedica. Having first been briefed on the company's activities, they were given a tour of the labs where they had the opportunity to see the latest in analytical technology used by Remedica and to discuss employment and career opportunities. ■



# A glimpse of Cyprus: Holy Monastery of Kykkos

The holy monastery of Kykkos is one the three largest and most ancient in Cyprus, which still houses a community of monks only, and belongs to the Church of Cyprus. It is also one of 5 monasteries of the Holy Cross in Cyprus which has the Bishop of Kykkos as its head. At the monastery, there is the famous painting of Holy Mother (Mary) the Blesser (of Kykkos) picturing her holding baby Jesus on the right hand side and according to tradition it is believed to have been painted by Luc the Evangelist. The painting, framed in silver, lies in a case made of tortoiseshell and mother-of-pearl, lies in front of the iconostasis.

The holy, basilica (royal), patriarch monastery of the Holy Cross of Holy Mary of Kykkos is situated in the Olympus mountains at a spot of the same name, in the western side of the Troodos mountain range near Throni of Panayia (the little throne of the Holy Mother) at an altitude of 1300m. It is called basilica (royal) because it was built with financial aid from the Byzantine Emperor Alexis the 1<sup>st</sup> and Great Komninos (1081 – 1118) who also sent the painting of the Holy Mother which up to that time had lain in the royal byzantine palace in Constantinople. The title Patriarch Monastery of the Holy Cross was conferred upon it in 1818, following a decree by the Ecumenical Patriarch Cyril the 6<sup>th</sup>.

According to legend the Cypriot hermit Isaiah miraculously saved the Emperor's daughter from an incurable disease. As a reward, he asked for the painting of the Holy Mother kept

in the Emperor's palace in Constantinople to be sent to Cyprus. Although saddened by the potential loss of his valuable treasure, the Emperor did send it to Cyprus with all due honours along with money to pay for the construction of a monastery where the painting would be kept. As the gift was subsequently validated by an imperial statute, the monastery is considered to have been established by royal decree.

During the times when Cyprus was under Turkish occupation (16<sup>th</sup> to 19<sup>th</sup> centuries), the monastery served as a spiritual centre and remains so today. For its important contribution to the general spiritual advancement of Cyprus, the monastery has been honoured by the Academy of Athens. In 1974, during the latest Turkish invasion of Cyprus, the monastery offered great help to refugees left without shelter.

The monastery houses a remarkable museum with exhibits that include church utensils, clothing, paintings, religious artefacts as well as an extensive library containing many books and manuscripts.

Today the brotherhood has a significant number of monks led by his holiness the Right Reverend Metropolitan of Kykkos and Tillyria monsignor Nikiforos. It is also the seat of the Kykkos Bishopric. Cyprus's first president, Archbishop Makarios the 3<sup>rd</sup>, served at the monastery as a cadet monk. In accordance

with his last wishes, he was buried at the top of Throni, three kilometres west of the monastery and not far from his place of his birth, the village of Panayia.

The monastery produces zivania (the traditional Cyprus white spirit) and a variety of other alcoholic drinks and also holds religious festivals on the 8<sup>th</sup> September (birthday of the Holy Mother) and on the 15<sup>th</sup> August (Assumption of the Holy Mother).

In addition, in the current Holy Synod of the Church of Cyprus, the Bishops of Kyrenia (Chrysostomos), Kykkos (Nikiforos) and Tamasos (Isaiah) are considered spiritual children of the Kykkos Monastery.

The head of the holy monastery of Kykkos and Bishop of Kykkos and Tillyria, Nikiforos, is an outstanding personality of contemporary Orthodox Church of Cyprus with a multi-faceted and multi-dimensional spiritual, cultural, and social contribution. ■

#### References:

- Wikipedia
- Cyprus Tourism Organisation
- [www.kykkos.org.cy](http://www.kykkos.org.cy)

